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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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10/071,499

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Neil M. Wolfman

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EXAMINER

WOODWARD, CHERIE MICHELLE

ART UNIT

PAPER NUMBER

1647

DATE MAILED: 05/10/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/071,499	WOLFMAN ET AL.	
	Examiner	Art Unit	
	Cherie M. Woodward	1647	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☐ Responsive to communication(s) filed on 06 March 2006.
- 2a) ☒ This action is **FINAL**. 2b) ☐ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 33-35, 38, 42-48, 50-59, 119-132, 137-142 and 144-173 is/are pending in the application.
- 4a) Of the above claim(s) 33-35, 38, 42-48, 50-59 and 137-142 is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 119-132 and 144-173 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on _____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some * c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____.
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).
- * See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- | | |
|---|---|
| 1) <input checked="" type="checkbox"/> Notice of References Cited (PTO-892) | 4) <input type="checkbox"/> Interview Summary (PTO-413) |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948) | Paper No(s)/Mail Date. _____ |
| 3) <input type="checkbox"/> Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) | 5) <input type="checkbox"/> Notice of Informal Patent Application (PTO-152) |
| Paper No(s)/Mail Date _____ | 6) <input type="checkbox"/> Other: _____ |

DETAILED ACTION

Formal Matters

1. Applicant's Remarks, filed 6 March 2006, are acknowledged. Claims 33-35, 38, 42-48, 50-59, 119-132, 137-142, and 144-173 are pending. Claims 33-35, 38, 42-48, 50-59, and 137-142 are withdrawn from consideration as being drawn to a non-elected invention. Claims 119-132 and 144-173 are under examination. The text of those sections of Title 35, U.S. Code, not included in this action can be found in a prior office action.

Response to Arguments

Claim Objections/Rejections Withdrawn

2. The rejection of claims 153-159 under 35 USC 102(a) as being anticipated by WO 200043781 is withdrawn in light of Applicants arguments, filed 6 March 2006.
3. The rejection of claims 119-132 under 35 USC 102(a) as being anticipated by WO 200043781 is withdrawn in light of Applicants arguments, filed 6 March 2006. Applicants assert that claim 119 (a) and (b) are subject to the wherein clause requiring a mutation that modifies the aspartate residue corresponding to Asp76 of SEQ ID NO: 5.
4. The rejection of claims 160-164 under 35 USC 103(a) as being unpatentable over WO 200043781 in view of US patent 5,723,125, is withdrawn in light of Applicants arguments, filed 6 March 2006.
5. The rejection of claims 128-130 and 160 under 35 U.S.C. 103(a) as being unpatentable over WO 200043781 in view of US patent 4,179,337 (Davis et al., 1979) is withdrawn in light of Applicants arguments, filed 6 March 2006.
6. The rejection of claims 121-126, 129-131, and 167-170 under 35 U.S.C. 103(a) as being unpatentable over WO 200043781 in view of U.S. patent 5,723,125 (Chang et al., 1998; see the 1449 submitted 24 June 2005) is withdrawn in light of Applicants arguments, filed 6 March 2006.
7. The rejection of claims 127, 129-130, and 160 under 35 U.S.C. 103(a) as being unpatentable over WO 200043781 in view of US patent 5,116,944 (Simvan *et al.*, 1992) is withdrawn in light of Applicants arguments, filed 6 March 2006.

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8. The rejection of claims 119-132 and 144-173 under 35 U.S.C. 103(a) as being unpatentable over WO 200043781 in view of Lee *et al.* (1990 J Biol Chem 265(35):21992-21996) is withdrawn in light of Applicants arguments, filed 6 March 2006.

Claim Objections/Rejections Maintained

Information Disclosure Statement

9. Applicants' arguments related to the Examiner declining to consider the International Search Reports, filed in the Information Disclosure Statement (IDS) of 13 March 2003, for non-conformance with MPEP 609, are acknowledged, but are not persuasive. The IDS citing the International Search Report fails to comply with 37 CFR 1.98(a)(1), which requires the following: (1) a list of all patents, publications, applications, or other information submitted for consideration by the Office; (2) U.S. patents and U.S. patent application publications listed in a section separately from citations of other documents; (3) the application number of the application in which the information disclosure statement is being submitted on each page of the list; (4) a column that provides a blank space next to each document to be considered, for the examiner's initials; and (5) a heading that clearly indicates that the list is an information disclosure statement.

If Applicants wish to have the individual references from the International Search Reports considered, to the extent that individual references cited therein have not already been considered, Applicants are encouraged to submit an IDS in accordance with 37 CFR 1.98 and MPEP 609, listing each reference individually, so that each individual reference may be considered by the Examiner.

Claim Rejections - 35 USC § 112, First Paragraph - Enablement

10. The rejection of claims 119-132 and 144-173 under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement, is maintained for the reasons of record in the Office Action of 7 September 2005 and for the reasons below. The claims recite a modified GDF-8 propeptide comprising (a) an amino acid sequence that is at least 75% identical to SEQ ID NO: 5 or (b) a fragment of the amino acid sequence of (a), wherein the modified GDF-8 propeptide has a mutation that modifies the aspartate residue corresponding to Asp76 of SEQ ID

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NO: 5, and wherein the modified GDF-8 propeptide has an increased *in vivo* or *in vitro* half-life relative to a corresponding unmodified GDF-8 propeptide; and wherein the modified GDF-8 propeptide inhibits one or more GDF-8 activities chosen from the recited group.

Applicants argue that the Examiner has misinterpreted the claims and that “[t]he term ‘modified GDF-8 propeptide’ is specifically defined in the claims as a GDF-8 propeptide having a specific modification in the aspartate residue corresponding to Asp76 of SEQ ID NO: 5 and an increased *in vivo* or *in vitro* half-life relative to a corresponding unmodified GDF-8 propeptide. Applicants also refer to the use of the term “modified GDF-8 propeptide” in the specification at p. 9, lines 18-29 and at p. 19, lines 23-29.

The independent claims 119, 144, 165, 171, and 173 all recite “a modified GDF-8 propeptide comprising...” Claim 119, for example, recites that this modified GDF-8 propeptide compris[es] “(a) an amino acid sequence that is at least 75% identical to SEQ ID NO: 5 or (b) a fragment of the amino acid sequence of (a)”. As written, the modified GDF-8 propeptide of claim 119 includes GDF-8 propeptides wherein the modification includes variation in 25% of the sequence identity of SEQ ID NO: 5 or wherein the modification includes fragmenting the GDF-8 propeptide into any given fragment. Claim 119 also recites the limitation that the “modified GDF-8 propeptide” also has a mutation that modifies the aspartate residue corresponding to Asp76 of SEQ ID NO: 5. Thus, the claim, as written, provides for initial modifications of a GDF-8 propeptide as a percent sequence identity variation or fragmentation and an additional modification of a specific amino acid residue, Asp76.

Additionally, claim 144, for example, recites “a modified GDF-8 propeptide comprising (a) a GDF-8 moiety comprising (i) an amino acid sequence that is at least 75% identical to SEQ ID NO: 5 or (ii) a fragment of the amino acid sequence of (i), and (b) an optional heterologous moiety...” As written, the modified GDF-8 propeptide of claim 144 includes GDF-8 propeptides wherein the modification includes a GDF-8 moiety with variation in 25% of the sequence identity of SEQ ID NO: 5 or wherein the modification includes fragmenting the GDF-8 propeptide into any given fragment. Claim 144 also recites the limitation that the “modified GDF-8 propeptide” contain an undisclosed optional heterologous moiety, and also has a mutation that modifies the aspartate residue corresponding to Asp76 of SEQ ID NO: 5. Thus, the claim, as written, provides for initial modifications of a GDF-8 propeptide as a percent sequence identity variation or fragmentation, an optional addition of a heterologous moiety that is not taught, and a modification of a specific amino acid residue, Asp76.

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The specification teaches the term “modified GDF-8 propeptide” at p. 9, lines 18-25 as “a GDF-8 inhibitor which comprises a modified GDF-8 propeptide, fragment or variant thereof which retains one or more biological activities of a GDF-8 propeptide and further comprises a stabilizing modification as set forth herein. Variant forms of GDF-8 propeptide, include, but are not limited to, for example, GDF-8 propeptides that have been modified to include mutations (including insertion, deletion, and substitution of amino acids) in the signal peptide or propeptide proteolytic cleavage sites to make the sites less susceptible to proteolytic cleavage.” Thus, Applicants’ definition of “modified GDF-8 propeptides” in the specification contradict the statement in Applicants Response of 6 March 2006. According to the teaching in the specification, as filed, the term modified does refer to undefined structural features that “include mutations (including insertion, deletion, an substitution of amino acids) in the signal peptide or propeptide proteolytic cleavage sites.

As such, the terms “modified” and “modifies” do not limit the possible modifications to the GDF-8 propeptide or a fragment thereof, nor do they limit the potential modifications to the aspartate residue at position 76. The skilled artisan would not be able to determine how this peptide was to be modified and thus would not be able to determine what Applicants intended the modifications to encompass. Further, because there are no functional limitations, apart from the inherent activities of the GDF-8 propeptide, one of skill in the art would not be able to determine the extent of modification that would be tolerated. The specification fails to provide guidance on what other kinds of modifications are to be made to residues other than the aspartate residue at position 76, if any (i.e. in terms of mutations of 25% sequence identity to SEQ ID NO: 5, fragments of the amino acid sequence of the sequence encompassing mutations of 25% sequence identity of SEQ ID NO: 5, additions of optional heterologous moieties), and offer only an invitation for further experimentation (see specification p. 9, lines 22-24).

Applicants also argue that the increased half-life of the modified propeptide is not an inherent property of the unmodified GDF-8 propeptide and that it is incorrect to posit that claims 119-132 and 114-173 merely encompass an amino acid sequence that is at least 75% identical to SEQ ID NO: 5. Applicants argue that all modified GDF-8 propeptides encompassed by the claims include a specific mutation at Asp76 and specific functional characteristics not present in the native GDF-8 propeptides. Applicants’ arguments have been fully considered, but are not persuasive.

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The Examiner recognizes that the limitations of the claims extend beyond the encompassing of a modified GDF-8 propeptide comprising an amino acid sequence that is at least 75% identical to SEQ ID NO: 5. Although the claims are drawn to "A modified GDF-8 propeptide," the claims, as written, include more than just a single modification to Asp76. The other claimed modifications include significant sequence variance (up to as much as 25% amino acid sequence identity variance), fragments of these variant sequences, and optional heterologous moieties. The Examiner recognizes that dependent claims 147-159 further limit the at least 75% identical structural limitation to encompass 80% to 95% amino acid sequence identity to SEQ ID NO: 5. As such, Applicants fail to teach the multiple claimed modifications; such that the claimed modifications will result in modified GDF-8 propeptides that still retain the claimed function.

Applicants argue that GDF-8 is a well known protein is a member of the TGF- β superfamily and that the Examiner's rejection based on characterizations that it is well known in the art that many amino acid substitutions are generally possible in any given protein with the positions within the protein's sequence, the point where such amino acid substitutions can be made with a reasonable expectation of success are limited, is inappropriate.

Applicants' arguments are misplaced. There is no question of whether the amino acid sequence of GDF-8 was known in the art at the time of filing nor is there a question of whether GDF-8 is known in the art to be a member of the TGF- β superfamily. The rejection is based on the Applicants' failure to teach how to make or use the modified GDF-8 propeptide variants. The Bowie et al., and Wells et al., references were cited because they teach that regions of well-known peptides can only tolerate relatively conservative substitutions or no substitutions and still retain function. Additionally, Skoknick et al., Bork, and Doerks et al., were cited as teaching references that state that knowing the protein structure itself is insufficient to annotate specific details of protein function. By way of further teaching example references only and for further clarification of the Skoknick et al., Bork, and Doerks et al., references (previously cited), in the transforming growth factor (TGF) family, Vukicevic et al. (1996, PNAS USA 93:9021-9026) disclose that OP-1, a member of the TGF- β family of proteins, has the ability to induce metanephrogenesis, whereas closely related TGF- β family members BMP-2 and TGF-1 had no effect on metanephrogenesis under identical conditions (p. 9023, paragraph bridging columns 1-2). See also, Massague, who reviews other members of the TGF- β family (1987, Cell 49:437-8, especially p. 438, column 1, second full paragraph to the end). Similarly, PTH and PTHrP are

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two structurally closely related proteins which can have opposite effects on bone resorption (Pilbeam et al., 1993, Bone 14:717-720; see p. 717, second paragraph of Introduction). Finally, Kopchick et al. (U.S. Patent 5,350,836) disclose several antagonists of vertebrate growth hormone that differ from naturally occurring growth hormone by a single amino acid (column 2, lines 37-48).

Claim Rejections - 35 USC § 112, First Paragraph – Written Description

11. The rejection of claims 119-132 and 144-173 under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement, is maintained for the reasons of record in the Office Action of 7 September 2005 and for the reasons below.

Applicants' have failed to respond to the rejections under 35 USC 112, first paragraph, Written Description. Claims 119-132 and 144-173 are directed to amino acid sequences that are at least 75% identical to SEQ ID NO: 5 and fragments thereof. In the instant case, Applicant's have not adequately described what changes to make to establish 75% sequence identity with SEQ ID NO: 5 or fragments. Applicants have not adequately described which critical residues must be maintained as for function of the protein. The skilled artisan would not be able to determine the extent of modifications that would be tolerated because there are no functional limitations specified with regard to proteins that are at least 75%, 85% or 95% identical to SEQ ID NO: 5 or fragments thereof. The claimed subject matter must be described in the specification to ensure that applicant had in his possession, as of the filing of the application, the specific subject matter claimed. See *In re Wertheim*, 541 F.2d 257, 191 USPQ 90 (CCPA 1976). A disclosure in an application, to be complete, must contain such description and details as to enable any person skilled in the art or science to which the invention pertains to make and use the invention as of its filing date. *In re Glass*, 492 F.2d 1228, 181 USQ 31 (CCPA 1974).

Applicant is reminded that *Vas-Cath, Inc. v. Mahurkar*, 935 F.2d 1555, 19 USPQ2d 1111 (Fed. Cir. 1991) makes clear that the written description provision of 35 U.S.C. 112 is severable from its enablement provision (see page 1115).

NO CLAIM IS ALLOWED.

12. **THIS ACTION IS MADE FINAL.** Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

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A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Cherie M. Woodward whose telephone number is (571) 272-3329. The examiner can normally be reached on Monday - Thursday 9:00am-7:30pm (EST).

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Brenda Brumback can be reached on (571) 272-0961. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

CMW


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